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(11)

**EP 1 260 505 A1**

(12)

**EUROPEAN PATENT APPLICATION**

(43) Date of publication:  
27.11.2002 Bulletin 2002/48

(51) Int Cl.7: **C07D 211/22**

(21) Application number: **02010234.9**

(22) Date of filing: **16.05.2002**

(84) Designated Contracting States:  
**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU**  
**MC NL PT SE TR**  
Designated Extension States:  
**AL LT LV MK RO SI**

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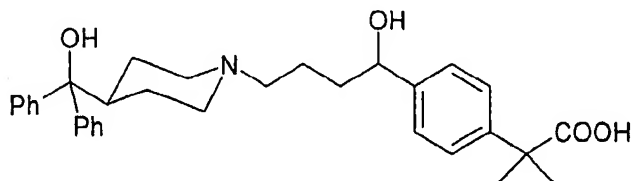
(30) Priority: 17.05.2001 IT RM20010260

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(54) **A process for the preparation of**  
**4-[1-hydroxy-4-(4-(hydroxydiphenylmethyl)-1-piperidinyl)-butyl]-alpha,**  
**alpha-dimethylbenzeneacetic acid**

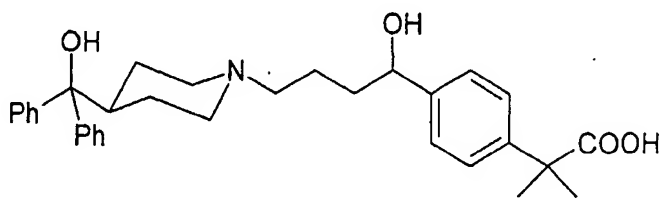
(57) A process for the preparation of 4-[1-hydroxy-4-(4-(hydroxydiphenylmethyl)-1-piperidinyl)-butyl]- $\alpha,\alpha$ -dimethylbenzeneacetic acid (Fexofenadine) of formula



**EP 1 260 505 A1**

**Description**

[0001] The present invention relates to a process for the preparation of 4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]- $\alpha,\alpha$ -dimethylbenzeneacetic acid, of formula (7):



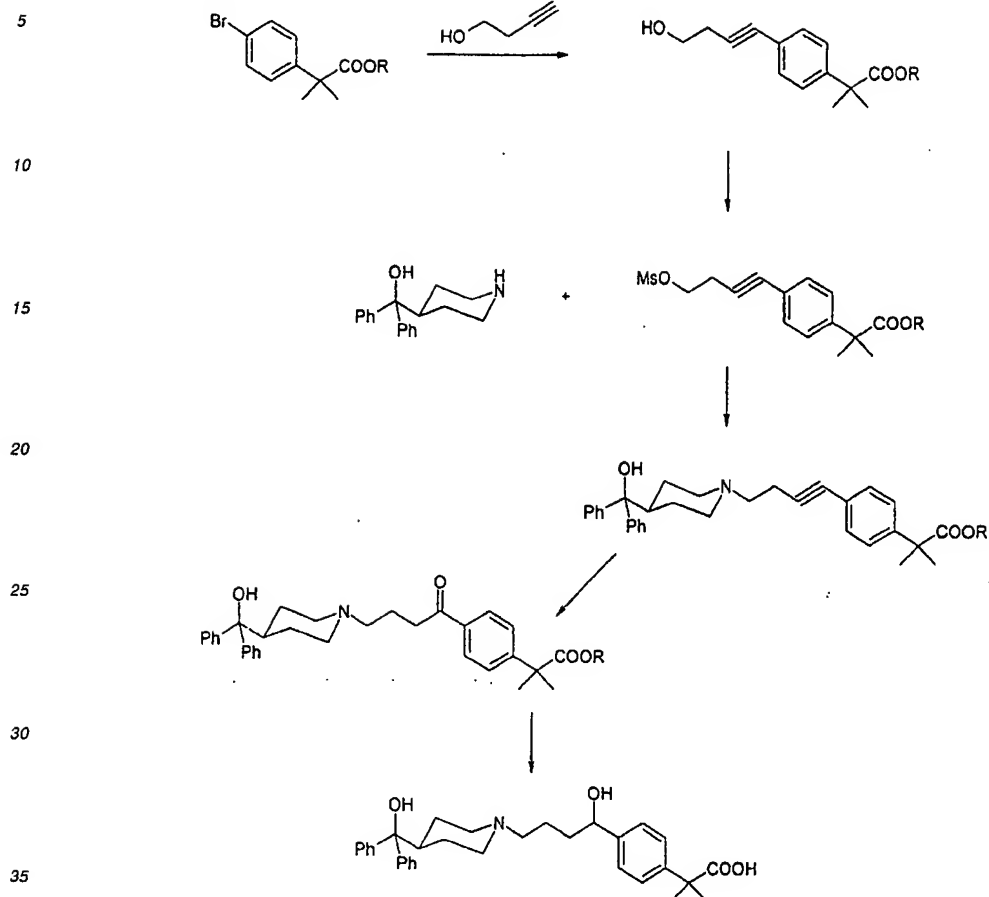
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**PRIOR ART**

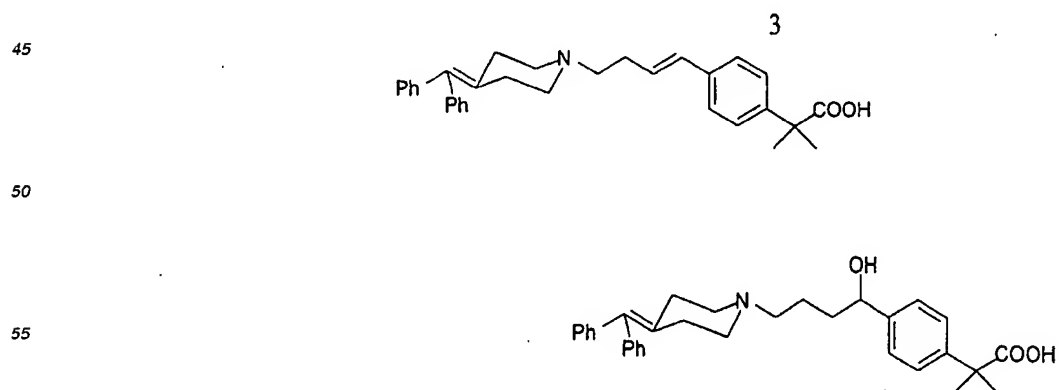
[0002] A number of processes for the preparation of Fexofenadine (W093/21156, W097/22344 W097/23213) are known. All said processes are characterized by a high number of steps. None of the known processes envisages a convergent approach, on the contrary the final molecule is obtained through the stepwise introduction of the various functions, starting from  $\alpha,\alpha$ -dimethylbenzeneacetic acid.

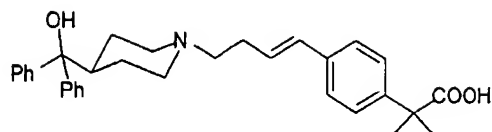
[0003] A process is also known (*J.Org.Chem.* 1994, 59, 2620-2622) which is shown in the following scheme 1:

Scheme 1



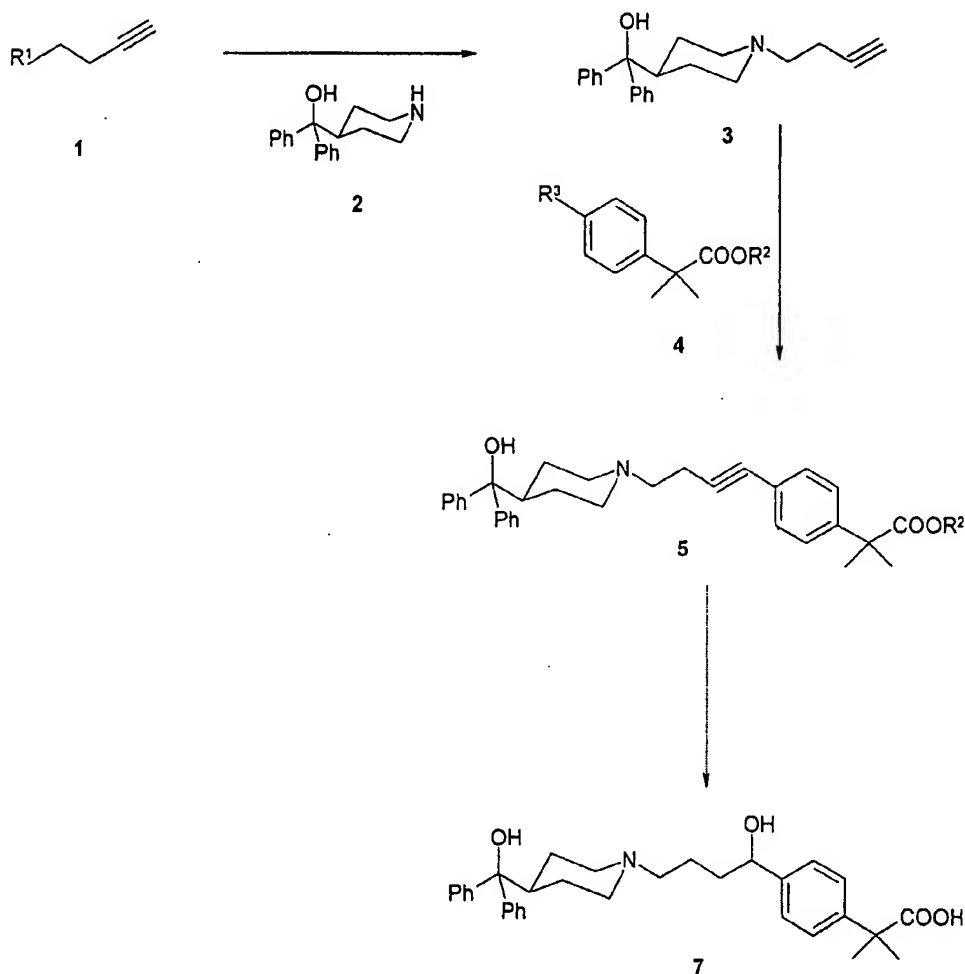
[0004] This process suffers from some disadvantages which prevent its industrial application: the oxidation of the triple bond to ketone involves the use of mercuric oxide under strongly acidic conditions, which give rise to dehydration by-products, whose formulae are reported in the following, said by-products being difficult to remove from the final product.





[0005] An advantageous process for the preparation of Fexofenadine has now been found, as reported in the following scheme 2:

Scheme 2



[0006] The process of the invention comprises reacting a compound (1) wherein R<sup>1</sup> is halogen (chlorine, bromine, iodine) or an alkyl or arylsulfonate group (methanesulfonyl, trifluoromethanesulfonyl, p-toluenesulfonyl and the like) with the compound of formula (2), to give the compound (3).

[0007] The reaction is carried out in protic solvents such as water, methanol, ethanol, isopropanol; aprotic dipolar solvents such as acetonitrile, dimethylformamide, dimethylsulfoxide; ethers such as tetrahydrofuran, dibutyl ether, dioxane; esters such as ethyl acetate, butyl acetate; aromatic solvents such as toluene, xylene, benzene; chlorinated solvents such as methylene chloride, chloroform, carbon tetrachloride or mixtures thereof in the presence of an inorganic (carbonates, bicarbonates, alkali or alkaline-earth hydroxides) or organic base (triethylamine, diisopropylethyl-

amine, azacyclonol, and the like) at temperatures ranging from 20°C to the reflux temperature of the solvent.

[0008] Compound (3), which is novel and is a further object of the invention, is then condensed with compound (4) in which R<sup>2</sup> is hydrogen or C1-C4 alkyl, and R<sup>3</sup> is halogen (chlorine, bromine, iodine) or an alkyl or arylsulfonate (methanesulfonyl, trifluoromethanesulfonyl, p-toluenesulfonyl and the like) in the presence of metal catalysts based on copper (I) or mixtures of palladium(0) and copper(I), in the presence of a base.

[0009] The Cu(I) catalyst can consist of copper salts having oxidation state 1, such as cuprous oxide, cuprous chloride, cuprous bromide, cuprous iodide, cuprous acetate, and the like.

[0010] The Pd(0) catalyst comprises palladium having oxidation state 0, elemental palladium (metal, cluster, and the like), supported palladium (for example on carbon), palladium complexed with suitable ligands, or palladium generated in situ by reduction of Pd(II) salts, such as palladium acetate, palladium chloride, and the like. Suitable ligands are, for example, phosphorous (III) or nitrogen derivatives. Examples of palladium complexes comprise:

bis-(triphenylphosphine)-dichloro complex  
 bis-(tributylphosphine)-dichloro complex  
 di-allyltriphenylphosphine-dichloro complex  
 tetrakis-(triphenylphosphine) complex  
 triphenylphosphine-piperidine-dichloro complex  
 bis-(triphenylphosphine)-diacetate complex  
 2,4-pentanedione complex  
 1,2-bis-(diphenylphosphine)-ethane complex bis-benzonitrile-dichloro complex.

[0011] The reaction is preferably carried out in the simultaneous presence of Pd(0), a phosphine ligand and Cu(I) salts, preferably in 1:4:2 Pd:ligand:Cu molar ratios. The palladium molar amount usually ranges from 0.01 to 0.1 relative to compound (3).

[0012] Alternatively, the reaction can be carried out in the presence of a Cu(I) salt and of a phosphine ligand in 1:2 Cu:ligand molar ratios. The copper molar amount usually ranges from 0.01 to 0.3 relative to compound (3).

[0013] The reaction is optionally carried out in the presence of a solvent selected from water-miscible alcohols, such as methanol, ethanol, isopropanol, 2-methoxy-1-propanol, N,N-dimethylformamide, dimethylsulfoxide, acetonitrile or mixtures thereof with water, in amounts ranging from 1 to 5 volumes relative to compound (3) at a temperature ranging from 20 to 150°C, preferably from 60 to 120°C.

[0014] Suitable bases are amino organic bases such as pyridine, piperidine, piperazine, morpholine, diisopropylethylamine, triethylamine, n-octylamine, and the like, preferably triethylamine or inorganic bases such as carbonates, bicarbonates, alkali or alkaline-earth oxides.

[0015] A further object of the present invention is the transformation of compound (5) into the corresponding compound (6), which is a precursor of Fexofenadine (7) (scheme 3), with a method which solves the problems described in J. Org. Chem. 1994, 59, 2620-2622, namely the formation of dehydration products due to the strongly acidic conditions.

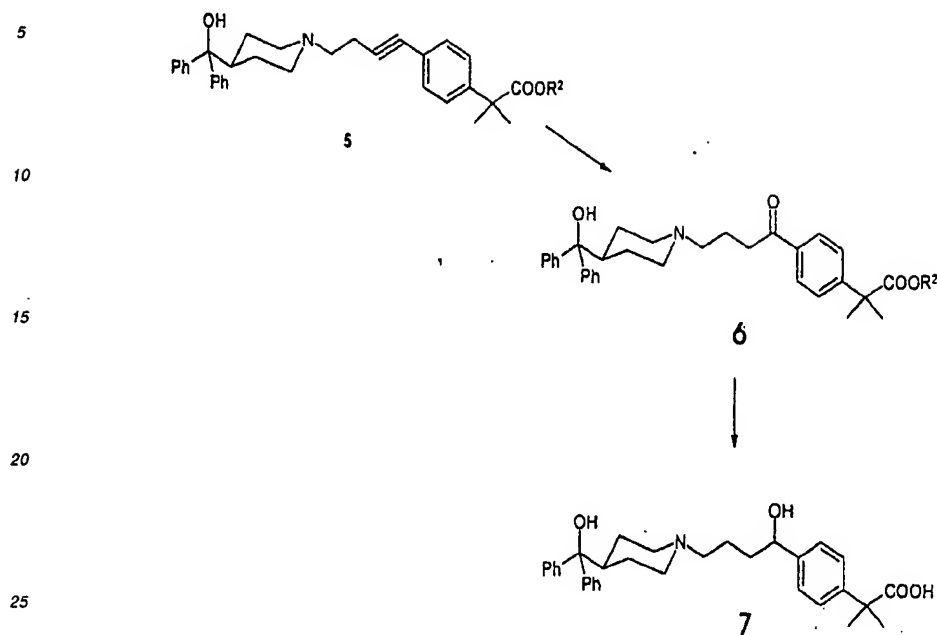
[0016] The transformation of compound (5) into compound (6) is carried out under neutral conditions in the presence of a catalyst based on palladium(II), platinum(II), ruthenium(III), optionally in the presence of ligands, or in the complexed form. Suitable ligands are phosphorous(III) derivatives, such as triphenylphosphine; nitrogen derivatives, such as benzonitrile, acetonitrile, EDTA or carbonyl derivatives such as carbon oxide, and the like.

[0017] The reaction is carried out in the presence of molar amounts of catalyst ranging from 0.005 to 0.1 relative to compound (5), preferably from 0.01 to 0.05.

[0018] The reaction is carried out in the presence of a water-miscible solvent, such as methanol, ethanol, isopropanol, tetrahydrofuran, N,N-dimethylformamide, acetonitrile, dimethylsulfoxide in amounts ranging from 1 to 5 volumes relative to compound (5), at a temperature ranging from 20 to 150°C, preferably from 60 to 120°C.

[0019] Compound (6) is subsequently transformed into Fexofenadine by hydrolysis of the ester and reduction with sodium borohydride, according to conventional conditions described in literature.

Scheme 3



[0020] The following examples illustrate the invention in greater detail.

Example 1: Preparation of Compound (1) (R<sup>1</sup>=OMs)

[0021] Methanesulfonyl chloride (57.3 g; 0.5 mols) is dropped under stirring into a solution 3-butyn-1-ol (35 g; 0.5 mols) and triethylamine (55.6 g; 0.55 mols) in methylene chloride (175 ml) keeping the temperature under 30°C. One hour after the addition, water is added (150 ml), the phases are separated, the organic phase is washed with water (100 ml) and concentrated to dryness under vacuum to obtain 1-methanesulfonyl-3-butyn (1) (R<sup>1</sup>=OMs) as an oily liquid (70.0 g; 94.6% yield).

[0022] <sup>1</sup>H NMR(CDCl<sub>3</sub>, TMS) δ (ppm): 2.06 (t, 1H); 2.65 (m, 2H); 3.05 (s, 3H); 4.30 (t, 2H).

Example 2: Preparation of Compound (3).

[0023] Azacyclonol (2) (56.1 g; 0.21 mols) is added to a solution of 1-methanesulfonyl-3-butyn (1) (R<sup>1</sup>=OMs) (14.8 g; 0.1 mols) in tetrahydrofuran (250 ml). The suspension is refluxed (68°C) under stirring for 20 hours. The mixture is then cooled to room temperature, filtered, and the azacyclonol methanesulfonate solid is washed with tetrahydrofuran (2x50 ml). The solution is concentrated under vacuum to a residue to yield the desired compound (3) as a viscous liquid (30.5 g; 95.5% yield).

[0024] <sup>1</sup>H NMR(DMSO, TMS) δ (ppm): 1.18 (m, 2H); 1.41 (m, 2H); 1.90 (t, 3H); 2.25 (m, 2H); 2.42 (m, 3H); 2.68 (t, 1H); 2.80 (m, 2H); 7.0-7.6 (aromatics, 10H).

Example 3: Preparation of compound (3).

[0025] Azacyclonol (2) (56.1 g; 0.21 mols) is added to a solution of 1-bromo-3-butynol (1) (R<sup>1</sup>=Br) (13.3 g; 0.1 mols) in tetrahydrofuran (250 ml). The suspension is refluxed (68°C) under stirring for 20 hours. The reaction mixture is cooled to room temperature and filtered, and the solid azacyclonol hydrobromide is washed with tetrahydrofuran (2x50 ml). The solution is concentrated to a residue to yield the desired compound (3) as a viscous liquid (30.7 g; 96.1% yield).

[0026] <sup>1</sup>H NMR(DMSO, TMS) δ (ppm): 1.18 (m, 2H); 1.41 (m, 2H); 1.90 (t, 3H); 2.25 (m, 2H); 2.42 (m, 3H); 2.68 (t, 1H); 2.80 (m, 2H); 7.0-7.6 (aromatics, 10H).

**Example 4:** Preparation of 4-[(4-hydroxydiphenylmethyl)-1-piperidinyl]-1-butynyl]- $\alpha,\alpha$ -dimethylbenzeneacetic acid methyl ester (5).

[0027] Palladium chloride (17.7 mg; 0.1 mmoles), triphenylphosphine (105 mg; 0.4 mmoles) and copper iodide (38 mg; 0.2 mmoles) are added in sequence to a solution of compound (3) (31.9 g; 0.1 mols) and  $\alpha,\alpha$ -dimethyl-(4-bromophenyl)acetic acid methyl ester (4) ( $R^2=Me$ ,  $R^3=Br$ ) (25.7 g; 0.1 mols) in triethylamine (120 ml). The mixture is refluxed for 18 hours. The resulting mass is concentrated to a residue under vacuum and diluted with methylene chloride (300 ml) and water (100 ml). The phases are separated and the organic phase is concentrated to a residue, to obtain a solid which is purified by silica gel chromatography (eluent n-heptane:ethyl acetate in 70:30 ratio) to yield the desired compound (5) (40.0 g; 80.7% yield).

[0028]  $^1H$  NMR(DMSO, TMS)  $\delta$  (ppm): 1.20 (m, 2H); 1.22 (s, 6H); 1.44 (m, 2H); 1.90 (t, 3H); 2.30 (m, 3H); 2.44 (m, 1H); 2.84 (m, 2H); 3.56 (m, 3H); 7.0-7.9 (aromatics, 14H).

**Example 5:** Preparation of 4-[(4-hydroxydiphenylmethyl)-1-piperidinyl]-1-butynyl]- $\alpha,\alpha$ -dimethylbenzeneacetic acid methyl ester (5).

[0029] Palladium chloride (17.7 mg; 0.1 mmoles), triphenylphosphine (105 mg; 0.4 mmoles) and copper iodide (38 mg; 0.2 mmoles) are added in sequence to a solution of (3) (31.9 g; 0.1 mols) and  $\alpha,\alpha$ -dimethyl-(4-trifluoromethylsulfonylphenyl)acetic acid methyl ester (4) ( $R^2=Me$ ,  $R^3=OSO_2CF_3$ ) (31.0 g; 0.1 mols) in triethylamine (120 ml). The mixture is refluxed for 18 hours. The resulting mass is concentrated to a residue under vacuum and diluted with methylene chloride (300 ml) and water (100 ml). The phases are separated and the organic phase is concentrated to a residue, to obtain a solid which is purified by silica gel chromatography (eluent n-heptane:ethyl acetate 70:30 ratio) to yield the desired compound (5) (35.7 g; 72.0 % yield).

[0030]  $^1H$  NMR(DMSO, TMS)  $\delta$  (ppm): 1.20 (m, 2H); 1.22 (s, 6H); 1.44 (m, 2H); 1.90 (t, 3H); 2.30 (m, 3H); 2.44 (m, 1H); 2.84 (m, 2H); 3.56 (m, 3H); 7.0-7.9 (aromatics, 14H).

**Example 6:** Preparation of 4-[(4-hydroxydiphenylmethyl)-1-piperidinyl]-1-butynyl]- $\alpha,\alpha$ -dimethylbenzeneacetic acid methyl ester (5).

[0031] Copper iodide (190 mg; 1 mmole), triphenylphosphine (524 mg; 2 mmoles) and potassium carbonate (27.6 g; 0.2 mmoles) are added in sequence to a solution of (3) (31.9 g; 0.1 mols) and  $\alpha,\alpha$ -dimethyl-(4-bromophenyl)acetic acid methyl ester (4) ( $R^2=Me$ ,  $R^3=Br$ ) (25.7 g; 0.1 mols) in N,N-dimethylformamide (100 ml). The mixture is refluxed for 10 hours. The resulting mass is concentrated to a residue under vacuum and diluted with methylene chloride (300 ml) and water (100 ml). The phases are separated and the organic phase is concentrated to a residue, to obtain a solid which is purified by silica gel chromatography (eluent n-heptane:ethyl acetate 70:30 ratio) to yield the desired compound (5) (41.1 g; 83% yield).

[0032]  $^1H$  NMR(DMSO, TMS)  $\delta$  (ppm): 1.20 (m, 2H); 1.22 (s, 6H); 1.44 (m, 2H); 1.90 (t, 3H); 2.30 (m, 3H); 2.44 (m, 1H); 2.84 (m, 2H); 3.56 (m, 3H); 7.0-7.9 (aromatic, 14H).

**Example 7:** Preparation of 4-[1-oxo-4-[4-hydroxydiphenylmethyl)-1-piperidinyl]butyl]- $\alpha,\alpha$ -dimethylbenzeneacetic acid methyl ester (6).

[0033] Platinum(II) chloride (532 mg; 2.0 mmoles) is added to a solution of (5) (49.5 g; 0.1 mols) in tetrahydrofuran (100 ml) and water (10 ml). The mixture is refluxed for 12 hours, then concentrated to a residue under vacuum and diluted with methylene chloride (300 ml) and water (150 ml). The phases are separated and the organic phase is concentrated to a residue, which is purified by silica gel chromatography (eluent methylene chloride:methanol = 15:1) to give the desired product 6 (43.6 g; 85% yield).

[0034]  $^1H$  NMR(CDCl<sub>3</sub>, TMS)  $\delta$  (ppm): 1.40 (m, 4H); 1.58 (s, 6H); 1.96 (m, 4H); 2.38 (t, 3H); 2.96 (m, 4H); 3.64 (s, 3H); 7.1+8.0 (aromatics, 14H).

**Example 8:** Preparation of Fexofenadine (7).

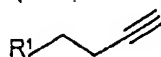
[0035] Sodium hydroxide (2.4 g, 0.06 mols) and sodium borohydride (0.8 g; 0.02 mols) are added to a solution of compound (6) (20.5 g; 0.04 mols) in methanol (100 ml) and water (30 ml). The mixture is heated at 50°C for 4 hours, then cooled to room temperature and added with acetone (5 ml). After 30 minutes, 36% hydrochloric acid (12.4 g; 0.122 mols) is added. The resulting suspension is heated to 45°C to complete dissolution, then is slowly cooled to 0°C. The resulting solid is filtered, washed with water (2x30 ml) and dried under vacuum at 60°C, to obtain Fexofenadine hydrochloride (15.5 g; 72% yield).

[0036]  $^1\text{H}$  NMR( $\text{CD}_3\text{OD}$ , TMS)  $\delta$  (ppm): 1.52 (s, 6H); 1.78 (m, 8H); 2.90 (m, 5H); 3.48 (d, 2H); 4.62 (t, 1H); 7.1-7.6 (aromatics, 14H).

5 **Claims**

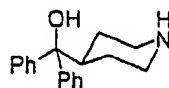
1. A process for the preparation of Fexofenadine, which comprises:

a) reaction of a compound of formula (1):



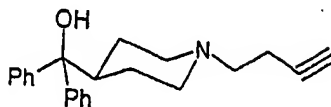
(1)

wherein  $\text{R}^1$  is a halogen or an alkyl or arylsulfonate group,  
with the compound of formula (2):



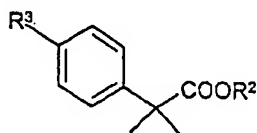
(2)

b) condensation of the resulting compound of formula (3):



(3)

with a compound of formula (4):

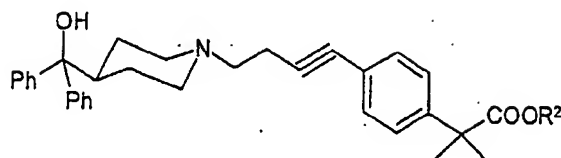


(4)

wherein  $\text{R}^2$  is hydrogen or C1-C4 alkyl, and  $\text{R}^3$  is a halogen or an alkyl or arylsulfonate, in the presence of metal catalysts based on copper(I) or mixtures of palladium(0) and copper(I) in the presence of a base;



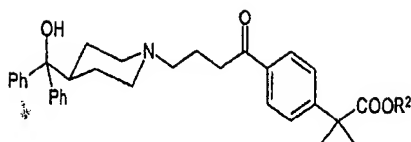
c) transformation of the resulting compound of formula (5):



(5)

into Fexofenadine, by addition of water and subsequent reduction of the carbonyl group to hydroxy group.

2. A process as claimed in claim 1, wherein the reaction of step a) is carried out in protic solvents, dipolar aprotic solvents, ethers, esters, aromatic solvents, chlorinated solvents or mixtures thereof in the presence of an inorganic or organic base temperatures ranging from 20°C to the reflux temperature of the solvent.
3. A process as claimed in claim 1 or 2, wherein the Pd(0) catalyst used in step b) comprises palladium having oxidation state 0, elemental palladium, supported palladium, palladium complexed with suitable ligands, or palladium generated in situ by reduction of Pd(II) salts.
4. A process as claimed in claim 1 or 2, wherein the Cu(I) catalyst is selected from cuprous oxide, cuprous chloride, cuprous bromide, cuprous iodide, cuprous acetate.
5. A process as claimed in claim 3, wherein the Pd(0) complex is selected from:
  - bis-(triphenylphosphine)-dichloro complex
  - bis-(tributylphosphine)-dichloro complex
  - di-allyltriphenylphosphine-dichloro complex
  - tetrakis-(triphenylphosphine) complex
  - triphenylphosphine-piperidine-dichloro complex
  - bis-(triphenylphosphine)-diacetate complex
  - 2,4-pentanedione complex
  - 1,2-bis-(diphenylphosphine)-ethane complex
  - bis-benzonitrile-dichloro complex.
6. A process as claimed in any one of claims 1 to 4, wherein the Pd:ligand:Cu molar ratios are 1:4:2 and the molar amount of palladium used ranges from 0.01 to 0.1 relative to compound (3).
7. A process as claimed in any one of claims 3 to 5, wherein the reaction is optionally carried out in the presence of a solvent selected from water-miscible alcohols or mixtures thereof with water, in amounts ranging from 1 to 5 volumes relative to compound (3) at a temperature ranging from 20 to 150°C, preferably from 60 to 120°C.
8. A process as claimed in any one of claims 3 to 6, wherein the base is selected from pyridine, piperidine, piperazine, morpholine, diisopropylethylamine, triethylamine, n-octylamine.
9. A process as claimed in claim 7, wherein the base is triethylamine.
10. A process as claimed in claim 1, wherein compound (5) is converted into compound (6)

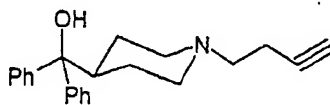


(6)

by treatment with water in the presence of a catalyst based on palladium, platinum or ruthenium, optionally in the presence of ligands.

11. A process as claimed in any one of the above claims, wherein compound (6) is transformed into Fexofenadine (7) by reduction with metal hydrides and hydrolysis of the ester groups.

12. As a new compound, the compound of formula (3)



(3)



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## EUROPEAN SEARCH REPORT

Application Number  
EP 02 01 0234

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Y,D	KAWAI S H ET AL: "A FACILE SYNTHESIS OF AN OXIDANT PRODUCT OF TERFENADINE" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 59, 1994, pages 2620-2622, XP002064406 ISSN: 0022-3263 *scheme 1* * page 2620, column 2 *	1-12	C07D211/22
Y	J.L.WRIGHT,T.F.GREGORY, C.F.BIGGE, P.A.BOXER,K.SERPA,L.T.MELTZER, L.D.WISE: "Subtype-selective N-Methyl-D-aspartate receptor Antagonists: Synthesis and Biological Evaluation of 1-(Arylalkynyl)-4-benzylpiperidines" J.MED.CHEM., vol. 42, 1999, pages 2469-2477, XP002205398 *scheme 1*	1-9,12	
Y,D	WO 97 23213 A (ALBANY MOLECULAR RES INC) 3 July 1997 (1997-07-03) * page 44; examples 7,10,12,14 *	11	TECHNICAL FIELDS SEARCHED (Int.Cl.7) C07D
Y	BAIDOSI W ET AL: "HYDRATION OF ALKYNES BY A PTCL4-CO CATALYST" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 62, no. 3, 7 February 1997 (1997-02-07), pages 669-672, XP000642974 ISSN: 0022-3263 * the whole document *	10	
The present search report has been drawn up for all claims			
Place of search MUNICH		Date of completion of the search 11 July 2002	Examiner Gavriliu, D
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

EPO FORM 1503 03.82 (Pot001)



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# EUROPEAN SEARCH REPORT

Application Number  
EP 02 01 0234

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Y	M.TOKUNAGA AND Y.WAKATSUKI: "The first Anti-Markovnikov Hydration of Terminal Alkynes: Formation of Aldehydes Catalysed by a Ruthenium(II)/Phosphane Mixture" ANGEW.CHEM.INT.ED., 1998, pages 2867-2869, XP002205399 *scheme 1* * page 2867 *	10	
			TECHNICAL FIELDS SEARCHED (Int.Cl.7)
The present search report has been drawn up for all claims			
Place of search MUNICH		Date of completion of the search 11 July 2002	Examiner Gavriliu, D
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone  Y : particularly relevant if combined with another document of the same category  A : technological background  O : non-written disclosure  P : intermediate document</p> <p>T : theory or principle underlying the invention  E : earlier patent document, but published on, or after the filing date  D : document cited in the application  L : document cited for other reasons  &amp; : member of the same patent family, corresponding document</p>			

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**ANNEX TO THE EUROPEAN SEARCH REPORT  
ON EUROPEAN PATENT APPLICATION NO.**

EP 02 01 0234

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.  
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11-07-2002

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